Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Rationale and design of a study to assess the safety and efficacy of rNAPc2 in COVID-19: the Phase 2b ASPEN-COVID-19 trial

Connie N. Hess, MD, MHS[a,b], Warren H. Capell, MD[a,b], Michael R. Bristow, MD, PhD[b,c], Wolfram Ruf, MD[d,e], Michael Szarek, PhD[a,b,f], David A. Morrow, MD, MPH[g], Jose C. Nicolau, MD, PhD[h], Christopher A. Graybill, PhD[c], Debra Marshall, MD[c], Judith Hsia, MD[a,b], and Marc P. Bonaca, MD, MPH[a,b] *Aurora, CO*

Background The interaction between thrombosis and inflammation appears central to COVID-19-associated coagulopathy and likely contributes to poor outcomes. Tissue factor is a driver of disordered coagulation and inflammatory signaling in viral infections and is important for viral replication; therefore, tissue factor may be an important therapeutic target in COVID-19.

Study Design ASPEN-COVID-19 (NCT04655586) is a randomized, prospective open-label blinded endpoint (PROBE), active comparator Phase 2b trial to evaluate the safety and efficacy of recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a potent tissue factor inhibitor, in patients hospitalized with COVID-19 with elevated D-dimer levels. This report describes the design of the Phase 2b dose ranging and proof of concept study. Participants are randomly assigned, in a 1:1:2 ratio, to lower or higher dose rNAPc2 by subcutaneous injection on days 1, 3, and 5 or to heparin according to local standard of care; randomization is stratified by baseline D-dimer level (at 2X upper limit of normal). The primary efficacy endpoint for Phase 2b is proportional change in D-dimer concentration from baseline to Day 8 or day of discharge, whichever is earlier. The primary safety endpoint is major or non-major clinically relevant bleeding through Day 8. Phase 2b enrollment began in December 2020 and is projected to complete ~160 participants by Q4 2021.

Conclusions ASPEN-COVID-19 will provide important data on a novel therapeutic approach that may improve outcomes in hospitalized COVID-19 patients beyond available anticoagulants by targeting tissue factor, with potential effects on not only thrombosis but also inflammation and viral propagation. (Am Heart J 2022;246:136–143.)

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 200 million people and caused more than 4 million deaths worldwide as of September 2021[1]. The underlying pathophysiology of COVID-19 appears to involve a severe inflammatory response and coagulopathy resulting in thrombosis despite conventional anticoagulation[2]. Pulmonary micro- and macrothrombi in conjunction with arterial and venous thrombi identified outside the lung indicate an aggressive hypercoagulable state characterized by elevated D-dimer[3-5]. Moreover, elevated plasma D-dimer has been associated with greater severity of disease and mortality in COVID-19[6]. Furthermore, prothrombotic autoantibodies, including pathogenic antiphospholipid antibodies, have been observed in COVID-19 and likened to a secondary antiphospholipid antibody syndrome[7-10].

Numerous randomized trials of available antithrombotic agents for prevention of clinical thrombotic events in patients with COVID-19 have targeted the intrinsic and/or common coagulation pathway[11]. Some have shown no benefit and have been associated with increased bleeding with higher intensity anticoagulation, while others have found a reduction in thrombotic risk when compared to prophylactic intensity anticoagulation among hospitalized patients with moderately severe disease[12]. To date, no survival benefit of therapeutic anticoagulation has been shown among patients with severe disease[13].

From the [a]CPC Clinical Research, Aurora, CO, [b]Department of Medicine, University of Colorado, Aurora, CO, [c]ARCA biopharma, Westminster, CO, [d]Johannes Gutenberg University Medical Center, Mainz, Germany, [e]Scripps Research, La Jolla, CA, [f]The State University of New York Downstate Health Sciences University, Brooklyn, NY, [g]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [h]Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

Submitted September 28, 2021; accepted December 21, 2021

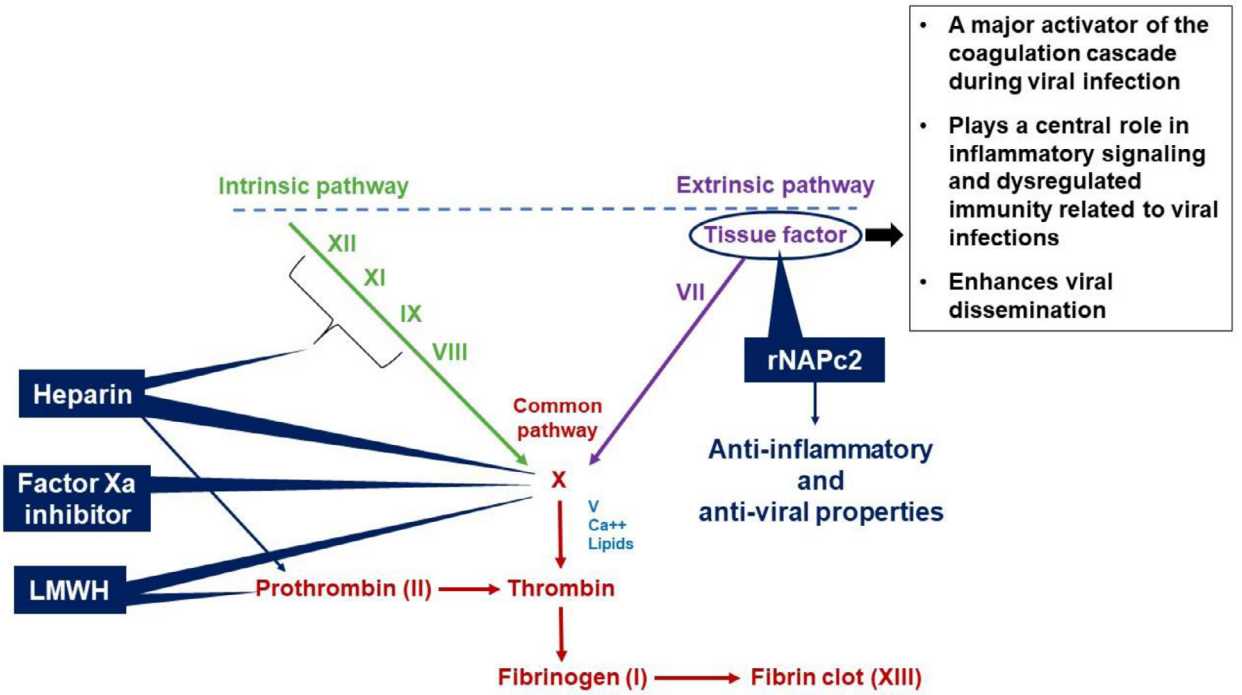
Reprint requests: Dr. Connie Hess, MD, MHS, 2115 N Scranton St. Suite 2040, Aurora, CO 80045-7120.

E-mail address: connie.hess@cpcmed.org.

0002-8703

https://doi.org/10.1016/j.ahj.2021.12.010

Figure 1



Anticoagulation targets in viral coagulopathy. Agents currently under study for reduction of thrombotic risk in COVID-19 all target either the intrinsic and/or common coagulation pathways. Recombinant nematode anticoagulant protein c2 (rNAPc2) inhibits tissue factor and the extrinsic pathway. Given the prominent role of tissue factor in the viral propagation and viral-induced hypercoagulability, tissue factor may offer a more precise target in COVID-19 to both prevent thrombotic events and reduce viral progression, potentially speeding recovery.

This limited efficacy of antithrombotic agents targeting the intrinsic/common pathway may be related to the observed activation of multiple pro-coagulant mediators, especially tissue factor, in hypercoagulability associated with viral infections such as with coronaviruses[14-17]. Tissue factor complexed with activated factor VII is responsible for not only initiating the extrinsic coagulation pathway, particularly during viral infections, but also activating members of the protease activated receptor family that are important in inflammatory disorders such as sepsis[14,18]. Incorporation of tissue factor into the viral envelope and involvement in viral dissemination have also been demonstrated in non-SARS-CoV-2 studies[19,20]. Therefore, tissue factor may provide a novel target in the viral-mediated hypercoagulability observed in COVID-19.

Recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a small recombinant protein cloned from the hematophagous hookworm *Ancyclostoma caninum,* is a potent and long-acting inhibitor of tissue factor, binding first to factor X (or factor Xa) and then to the factor VIIa/tissue factor catalytic complex, thereby inhibiting the extrinsic coagulation pathway (Figure 1) [21]. In Ebola-infected non-human primates treated with rNAPc2, reductions in D-dimer, inflammatory biomarker response, and viral load, and a trend for improvement in survival have been demonstrated[22]. Treatment with rNAPc2 in mice infected with Herpes simplex virus 1 reduces viral load[19]. Therefore, rNAPc2 has the potential to improve outcomes in COVID-19 through both anticoagulant and non-anticoagulant mechanisms, potentially improving disease recovery in hospitalized patients.

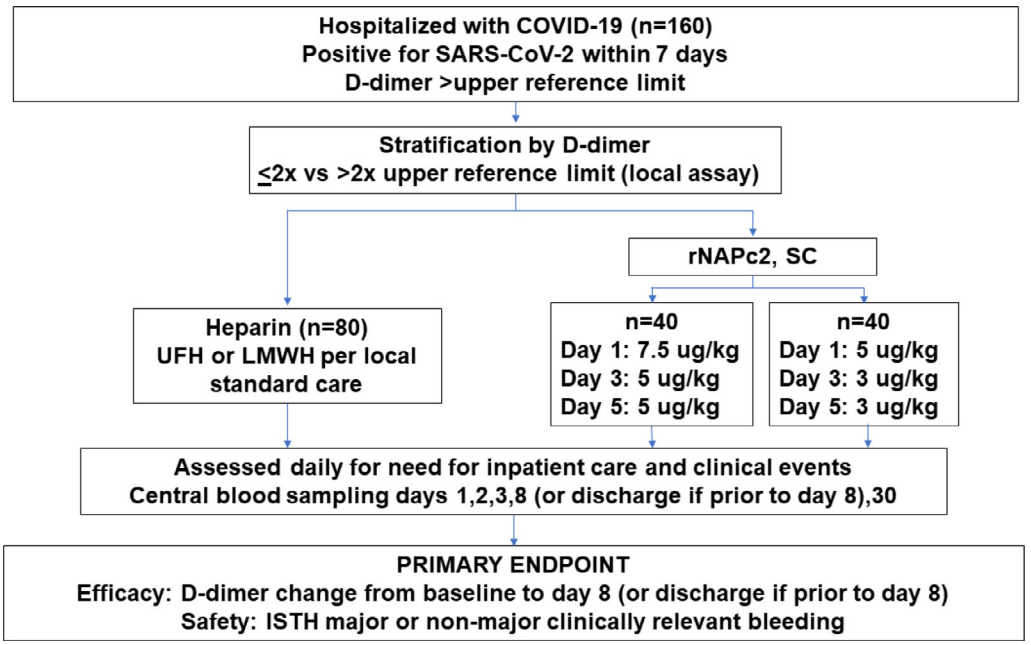
The Assessing Safety, hosPitalization and Efficacy of rNAPc2 in COVID-19 (ASPEN-COVID-19) study consists of sequential Phase 2b and Phase 3 trials designed to investigate the safety and efficacy of rNAPc2 in patients hospitalized with COVID-19 at elevated risk for thrombosis. The trial design for Phase 2b of ASPEN-COVID-19 is described herein.

Study design and population

The ASPEN-COVID-19 phase 2b study is a multicenter, prospective randomized, open-label blinded endpoint (PROBE) design, active comparator trial to assess the efficacy and safety of rNAPc2 compared with heparin in patients hospitalized with COVID-19 (Figure 2).

Selection criteria were designed to enroll a broadly representative population of adults hospitalized with

Figure 2



Study design for ASPEN-COVID-19 Phase 2b. ISTH, International Society of Haemostasis and Thrombosis; LMWH, low-molecular weight heparin; SC, subcutaneously; UFH, unfractionated heparin

COVID-19 at elevated thrombotic risk as reflected by elevated D-dimer. The study population was intended to include a range of disease severity, including critically ill patients requiring care in the intensive care unit and/or organ support., as well as patients managed with non-ICU-based care. Participants must be 18-90 years of age, weigh at least 50 kilograms, require inpatient medical care for COVID-19 as documented by a test indicating active infection, and have a systemic venous D-dimer plasma level elevated above the upper limit of normal per the local laboratory reference range. Key exclusion criteria include: high bleeding risk such as recent surgery, any medical indication for therapeutic anticoagulation, or concomitant use of dual antiplatelet therapy; significantly impaired renal function; inability to receive heparin (e.g. history of heparin-induced thrombocytopenia and thrombosis); and estimated life expectancy less than 72 hours. A complete list of inclusion and exclusion criteria is provided in Table I.

Randomization is completed through use of a central computerized system, and study drug assignment is concealed from investigators until after eligibility is confirmed. Although open-label, investigators are instructed to maintain participant blinding, if possible. Participants are randomized in a 1:1:2 ratio to receive higher dose and therapeutic level rNAPc2 (7.5 ug/kg by subcutaneous injection on day 1, followed by 5 ug/kg on days 3 and 5) approximating therapeutic anticoagulation[23], lower dose level rNAPc2 (5 ug/kg on day 1, followed by 3 ug/kg on days 3 and 5) providing intermediate dose anticoagulation[23], or heparin (low-molecular weight or unfractionated) administered according to local standard of care. Randomization is stratified by screening D-dimer concentration (less than or equal to vs. greater than twice the local laboratory upper reference limit).

Enrollment began in December 2020 and is expected to conclude in Q4 2021. The study is being conducted in accordance with all local laws and regulations and the ethical principles of the Declaration of Helsinki according to the International Council on Harmonization Good Clinical Practice guidelines. The study protocol and informed consent have been reviewed and approved by the corresponding health authorities, Institutional Review Boards, and Ethics Committees for all participating study sites. Enrolled participants provide informed consent for participation in the trial.

Treatment protocol and follow-up procedures

Treatment selection

The doses of rNAPc2 were selected to balance antithrombotic effects and bleeding risk based on data from over 700 participants in 3 separate phase 2 dose-ranging

Table I. ASPEN-COVID-19 Inclusion/Exclusion criteria

Inclusion criteria	
1.	Age ≥ 18 years and ≤ 90 years at the Screening assessment
2.	Weight ≥ 50 kg at randomization
3.	Hospitalized with a diagnosis of COVID-19 and in need of inpatient medical care
4.	Positive for SARS-CoV-2 on nasopharyngeal, oropharyngeal or other tissue/body fluid samples by PCR or validated other test of ongoing infection (not an antibody test for prior exposure), within 7 days of hospitalization or screening assessment
5.	D-dimer level > upper limit of normal at screening
6.	Provided electronic or written informed consent, either personally or through a legally authorized representative
7.	Must agree not to participate in a concurrent interventional study involving anticoagulation or anti-platelet therapy
8.	Female patients of reproductive or childbearing potential must be willing to use an effective method of contraception for the duration of the study, and male patients must be willing to use effective method of contraception to avoid partner pregnancy and abstain from sperm donation for at least 90 days after last dose
Exclusion criteria	
1.	High bleeding risk, e.g. major surgery within prior 1 month, history of a major bleed while receiving anticoagulation, recent hemorrhagic stroke, current or planned (during current hospitalization) dual anti-platelet therapy, platelet count <25,000/μL, current therapeutic anticoagulation for a medical indication other than COVID-19, e.g. atrial fibrillation, known thrombosis, hereditary or acquired coagulopathy treated with therapeutic anticoagulation. Patients receiving prophylactic anticoagulation are eligible if they are willing to discontinue current anticoagulation.
2.	Sustained systolic blood pressure < 90 mmHg considered to be clinically significant
3.	Persistent eGFR <20 ml/min/1.73m^2
4.	Known severe liver disease (e.g. bilirubin >3.5 mg/dL (60 umol/L))
5.	Life expectancy estimated to be < 72 hours based on current clinical condition
6.	Anticipated hospital discharge or transfer within 5 days based on current clinical condition
7.	Known anti-phospholipid syndrome
8.	Unable to receive heparin, e.g. history of heparin-induced thrombocytopenia and thrombosis (HITT)
9.	Participation in any interventional clinical study with an investigational product within 7 days of the Screening assessment or within 5 half-lives of the investigational agent, whichever is longer

studies examining rNAPc2 in patients with acute coronary syndrome[23], patients undergoing elective percutaneous coronary intervention[24], and patients following total knee arthroplasty[25]. Pharmacokinetic (PK) data from prior rNAPc2 trials have demonstrated a consistently long half-life that increases with repeat dosing, with escalating dose levels after both the second (Day 3) and third (Day 5) doses; in this model, steady state is not reached within 8 days. For ASPEN-COVID-19, a loading dose was included to rapidly attain rNAPc2 plasma levels approximating those achieved at steady state, as COVID-19 patients ill enough to be hospitalized are at immediate risk for the conditions that lead to micro- or macrovascular thromboses. Pharmacokinetic and pharmacodynamic studies following single doses of rNAPc2 demonstrated a dose dependent increase in international normalized ratio (INR) ranging from 1.5 at 3.0 μg/kg to 1.75 at 5.0 μg/kg and 2.1 at 7.5 μg/kg. Based on these data, an initial dose of 5 μg/kg followed by 3.0 μg/kg on Days 3 and 5 was estimated to be equivalent to prophylactic dose heparin. A dose of 7.5 μg/kg followed by 5 μg/kg on days 3 and 5 was estimated to correlate with a higher intensity of anticoagulation approximating therapeutic heparin. Given the ~50-hour half-life of rNAPc, clinical effects of rNAPc2 are expected to begin to decline by day 8. Therefore, subjects randomized to rNAPc2 may be given standard of care heparin therapy beginning on day 8 per the discretion of the investigator. Dose selection for Phase 3 will be based on data from this Phase 2b study.

Accumulating data linking COVID-19 to thrombotic events has shifted equipoise away from inclusion of a placebo group. Consequently, rNAPc2 will be compared to heparin administered per standard of care. In light of institutional and international variation in use of anticoagulation for thromboprophylaxis in patients hospitalized with COVID-19, heparin-allocated participants will receive regimens per clinical care teams and according to local institutional practice.

Concomitant therapies

The protocol allows for treatment with standard therapies according to local practice, including approved antiviral and anti-inflammatory therapies. The protocol disallows treatment with any drug therapy not approved for use in COVID-19. If treatments such as systemic anticoagulants or dual antiplatelet therapy that might increase bleeding risk when combined with the study treatments are required for clinical indications, study drug will be discontinued.

Visit schedule and follow-up

Participants will be closely followed while hospitalized, including recording of clinical/adverse events, concomitant medications, and the Adaptive COVID-19 Treatment Trial (ACTT) ordinal scale for each day until hospital discharge[26]. Blood samples will be obtained for central laboratory analysis of study biomarker endpoints on days 1 (prior to first study drug administration), 2, 3, 8

Table II. Safety and efficacy endpoints

Primary safety endpoint: CEC-adjudicated ISTH major or non-major clinically relevant bleeding through the earlier of Day 8 or two days after day of discharge if prior to Day 8. Each rNAPc2 dose will be compared with heparin-allocated patients.
Secondary safety endpoints:

- major or non-major clinically relevant bleeding with rNAPc2 vs. heparin through Day 30
- any bleeding through Day 8 and Day 30
- other adverse events

Primary efficacy endpoint: Proportional change in D-dimer level from baseline to Day 8 (or day of discharge if prior to Day 8) between the pooled rNAPc2 groups and the heparin group
Secondary efficacy endpoints:

- proportional change in D-dimer level from baseline to 24 hours post-dose (Day 2) and Day 3
- probability of discharge accompanied by ACTT ≥6 prior to Day 8
- change in biomarkers of inflammation and coagulation from baseline to Day 8 (or day of discharge if prior to Day 8)

Exploratory efficacy endpoints:

- Time to recovery defined as CEC-adjudicated ACTT score ≥6 by Day 30
- CEC-adjudicated clinical arterial and venous thrombotic events and death Healthcare resource utilization
- PCFS

ACTT, Adaptive COVID-19 Treatment Trial; CEC, clinical endpoint committee; ISTH, International Society on Thrombosis and Haemostasis; PCFS, Post-COVID Functional Status

(or day of discharge if prior to day 8), and 30. Blood will also be stored in a biorepository for future research for patients that consent to do so. The Post-COVID functional status (PCFS) scale will be assessed immediately after hospital discharge, if applicable, and on day 30[27]. For those participants discharged from the hospital prior to day 30, a final follow-up visit at 30 days will include assessment of clinical/adverse events, concomitant medications, ACTT ordinal scale, and vital status, in addition to other day 30 visit activities as listed above.

Study endpoints

The primary safety endpoint for the trial is International Society of Thrombosis and Haemostasis (ISTH) major or non-major clinically relevant bleeding through day 8 (or day of discharge if earlier than day 8), comparing each rNAPc2 dosing regimen against heparin-allocated patients. The primary efficacy endpoint is proportional change in D-dimer level from baseline to Day 8 (or day of discharge if prior to Day 8) that will be compared between the pooled rNAPc2 groups and the heparin group. A complete listing of study endpoints is provided in Table II. Clinical safety and efficacy events will be adjudicated by a blinded Clinical Events Committee (CEC) according to pre-specified definitions. Given the open-label trial design, blinded adjudication of these clinical endpoints is critical to reduce potential bias in the assessment of study outcomes.

Statistical considerations

Efficacy analyses will be conducted on all randomized patients using the principle of intention-to-treat; safety analyses will be conducted on all patients that received at least 1 dose of study drug and analyzed according to actual drug received. For the primary efficacy endpoint, proportional change in D-dimer, represented by percent change, will be based on data provided by the central laboratory paired samples. To reduce missingness, if the central laboratory values are not available, available paired local laboratory values will be used. Wilcoxon signed rank tests will be used to compare baseline vs. Day 8, or day of discharge if prior to day 8, values within each treatment group, and a Wilcoxon rank sum test will be used to compare proportional change from baseline to Day 8, or day of discharge if prior to day 8, between treatment groups. The primary outcome will be tested at a 2-sided significance level of 5%.

A sample size of ~100 subjects was originally planned to provide ~90% power for a pooled rNAPc2 vs heparin comparison assuming a standardized mean difference in D-dimer of 0.67 and a 2-sided Type 1 error of 5%. However, during ASPEN-COVID-19, clinical care for hospitalized COVID-19 patients has evolved to include use of concomitant therapies that might affect the primary D-dimer endpoint (e.g., steroids, remdesivir), COVID-19 vaccines that may modulate disease severity have been developed, and data have emerged regarding heterogeneity of antithrombotic therapies according to

severity of COVID-19[12,13]. In addition, data may be missing due to issues with laboratory sampling. Given these developments and to ensure adequate and evaluable primary endpoint data, the sample size was subsequently increased to ~160 subjects. This sample size provides adequate power (>80%) for the primary efficacy endpoint across a range of effect sizes, ensuring inferences for the primary endpoint analysis will be robust given potential confounding factors such as missing data (random or non-random), heterogeneous application of heparin (low molecular weight and unfractionated; prophylactic and therapeutic), effects of subject-level covariates (e.g., comorbidities), and site-level covariates (e.g., country).

An independent Data and Safety Monitoring Committee (DSMC) is responsible for monitoring the safety of study participants throughout the trial. An analysis of safety was conducted after enrollment of ~30 participants, and the DSMC recommended continuation of the trial. When approximately 120 subjects have reached Day 8, a futility analysis and a conditional power analysis will be conducted. The DSMC may consider additional factors and request additional analyses to make decisions on trial conduct.

Study organization

Phase 2b of ASPEN-COVID-19 is being conducted at up to 24 sites in the United States, Argentina, and Brazil. An Executive Committee is responsible for oversight of the study and will submit study results for publication in a peer-reviewed journal. The trial is sponsored by ARCA *biopharma*, Inc. (Westminster, CO, United States) and conducted in partnership with CPC Clinical Research (Aurora, CO), a non-profit Academic Research Organization affiliated with the University of Colorado. International trial support is also provided by Estudios Clínicos Latinoamérica (Rosario, Argentina), Hospital Israelita Albert Einstein (São Paulo, Brazil), and Atlantis Clinical (São Paulo, Brazil). ASPEN-COVID-19 is registered on clinicaltrials.gov under NCT04655586. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Discussion

While vaccination against SARS-CoV-2 is ongoing worldwide, clinicians continue to face challenges in caring for patients hospitalized with COVID-19. In addition to issues with vaccine production, distribution, and uptake, SARS-CoV-2 variants pose a further serious threat to progress in containment and treatment of COVID-19. Despite current anticoagulation regimens, substantial residual thrombotic risk remains, particularly among severely ill patients[13]. Furthermore, available anticoagulants may not address important processes such as inflammation and viral replication that contribute to COVID-19 associated morbidity and mortality. Ongoing efforts to mitigate thrombosis, inflammation, and viral dissemination have mainly focused on countering each of these processes individually. In contrast, rNAPc2 is a novel therapeutic with potential impact on all 3 and may therefore provide a therapy that more precisely addresses the pathophysiology underlying COVID-19.

ASPEN-COVID-19 is designed to assess the safety and efficacy of rNAPc2 in reducing thrombotic risk and potentially speeding recovery compared to standard of care thromboprophylaxis with heparin in patients hospitalized with COVID-19. rNAPc2 has shown an acceptable safety profile and antithrombotic promise in 3 completed Phase 2 studies. In subjects undergoing total knee replacement, rNAPc2 reduced the risk of deep venous thrombosis by as much as 50% more than historical rates observed with standard thromboprophylaxis, depending on the dose and timing of rNAPc2 administration[25]. When given to subjects undergoing elective coronary intervention and receiving peri-procedural heparin, a single dose of rNAPc2 resulted in prolonged suppression of thrombin generation for up to 36 hours[24]. In the setting of acute coronary syndrome, a condition with accelerated platelet activation and thrombin generation, rNAPc2 effectively suppressed thrombin generation and electrocardiogram evidence of ischemia[23]. Notably, these studies demonstrated acceptable bleeding rates in populations undergoing invasive procedures, often with concurrent antiplatelet and anticoagulant therapies.

In contrast to the numerous completed and ongoing trials of available anticoagulants, rNAPc2 represents a novel mechanism acting via the extrinsic coagulation pathway that might more precisely address the pathophysiology seen in COVID-19. The trial endpoints are predicated on the potential for rNAPC2 to modulate multiple facets of SARS-CoV2 infection – thrombosis, inflammation, and viral propagation. Tissue factor activates the coagulation cascade, potentiates viral infectivity, and mediates inflammation associated with viral illness through protease-activated receptor signaling and activation of toll-like receptors[28,29]. Importantly, the latter mechanism underlies viral triggering of cytokine storm in antiphospholipid syndrome[30]. Importantly, Ebola and herpes simplex virus animal models have demonstrated the ability of rNAPc2 to lower tissue factor activity, virus titers, D-dimer concentrations, and inflammatory markers, as well as potentially improve survival rates compared to animals treated with placebo[19,20,22]. The extent to which these preclinical studies may translate into clinical benefit for hospitalized patients with COVID-19 will be assessed in ASPEN-COVID-19.

In addition to hypercoagulable risk associated with viruses other than SARS-CoV-2, other potential applications for rNAPc2 include conditions such as cytokine storm associated with cancer therapies or antiphospho-

lipid antibody syndrome in which tissue factor may be a useful therapeutic target. The latter may be particularly relevant in the current study population, as pathogenic antiphospholipid antibodies operating through tissue factor have been observed in COVID-19[10,31]; ASPEN-COVID-19 may provide important insight into whether tissue factor inhibition with rNAPc2 can prevent formation of these antiphospholipid antibodies and potentially mitigate longer-term thrombotic risk. Finally, the additional clinical experience gained in ASPEN-COVID-19 will build on the promising antithrombotic effects already observed in venous thromboprophylaxis, acute coronary syndrome, and elective cardiovascular procedures, as well as other anticoagulant trials in COVID-19.

Summary

Effective treatments for hospitalized patients with COVID-19 remain an important unmet need. The ASPEN-COVID-19 Phase 2b study has been designed to evaluate the safety of the novel tissue factor inhibitor rNAPc2 and its effects on biomarkers of thrombotic risk and inflammation in patients requiring inpatient care for COVID-19. Translation of favorable preclinical effects on viral infectivity and virus-induced inflammation into clinical benefits will be assessed as exploratory endpoints.

Funding

ASPEN-COVID-19 is supported by a research grant from ARCA *biopharma*.

Disclosures

MRB reports he is an employee, officer, and director of ARCA *biopharma*; WR reports research support from ICONIC Therapeutic, consultant, intellectual property, and royalty income from ARCA *biopharma*, and ownership in MeruVasImmune; MS reports grant support from Sanofi, Regeneron, Esperion, CiVi, Lexicon, and Bayer and consulting fees from Resverlogix; DAM is a member of the TIMI Study group which has received institutional research grant support through Brigham and Women's Hospital from: Abbott Laboratories, Amgen, Anthos Therapeutics, ARCA *biopharma*, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, Janssen, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron, Roche, Siemens, and Zora Biosciences. DAM has also received consulting fees from Bayer Pharma, InCarda, Merck, Novartis, and Roche Diagnostics; JCN reports grant support from Amgen, AstraZeneca, Bayer, Esperion, CLS Behring, Dalcor, Daiichi Sankyo, Janssen, Novartis, NovoNordisk, Sanofi, and Vifor and honoraria/consulting fees from Daiichi Sankyo, Novartis, Sanofi, and Servier; CAG and DM report employment by ARCA biopharma; JH reports stock ownership in AstraZeneca stock. CNH, WHC, MS, JH, and MPB receive salary support from CPC Clinical research, a non-profit academic research organization affiliated with the University of Colorado, that receives research grant/consulting funding from: Abbott, Agios, Alexion Pharma, Alnylam, Amgen, Angionetics, ARCA Biopharma, Array, AstraZeneca, Atentiv, Audentes, Bayer, Better Therapeutics, Brigham and Women's Hospital, Bristol-Myers Squibb, Cardiol Therapeutics, CellResearch, Cook Medical, Cook, CSL Behring, Eidos Therapeutics, EP Trading Co, Esperion Therapeutics, EverlyWell, Faraday, Fortress Biotech, HDL Therapeutics, Heartflow, Hummingbird Bioscience, Insmed, Janssen, Kowa Research, Lexicon, Merck, Medtronic, Moderna, Novate Medical, NovoNordisk, Pfizer, PhaseBio, PPD Development, Prairie Education and Research, Prothena Biosciences, Regeneron, Regio Biosciences, Sanifit Therapeutics, Sanofi, Smith and Nephew, Stealth BioTherapeutics, University of Colorado, Worldwide Clinical Trials, Wraser, Yale Cardiovascular Research Group.

References

1. https://coronavirus.jhu.edu/map.html. Accessed on September 28, 2021.
2. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis 2020;50:54–67.
3. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383:120–8.
4. Vasquez-Bonilla WO, Orozco R, Argueta V, et al. A review of the main histopathological findings in the coronavirus disease 2019 (COVID-19). Hum Pathol 2020;105:74–83.
5. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med 2020;12:eabd3876. doi:10.1126/scitranslmed.abd3876.
6. Gungor B, Atici A, Baycan OF, et al. Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis. Am J Emerg Med 2021;39:173–9.
7. Piazza G, Morrow DA. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. J Am Med Assoc 2020;324:2548–9.
8. Cavalli E, Bramanti A, Ciurleo R, et al. Entangling COVID-19 associated thrombosis into a secondary antiphospholipid antibody syndrome: Diagnostic and therapeutic perspectives (Review). Int J Mol Med 2020;46:903–12.
9. Hollerbach A, Muller-Calleja N, Pedrosa D, et al. Pathogenic lipid-binding antiphospholipid antibodies are associated with severity of COVID-19. J Thromb Haemost 2021;19:2335–47.
10. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic antiphospholipid antibodies in COVID-19. medRxiv 2020;15. doi:10.1101/2020.06.15.20131607.
11. Azita H, Talasaz AH, Sadeghipour P, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC State-of-the-art review. J Am Coll Cardiol 2021;77:1903–21.
12. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically Ill patients with covid-19. N Engl J Med 2021;385:790–802.

13. The REMAP-CAP, ACTIV-4a and ATTACC Investigators. therapeutic anticoagulation with heparin in critically Ill patients with covid-19. N Engl J Med 2021;385:777–89.
14. Blasi A, von Meijenfeldt FA, Adelmeijer J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. J Thromb Haemost 2020;18:2646–53.
15. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020;127.
16. Mackman N, Grover SP, Antoniak S. Tissue factor expression, extracellular vesicles, and thrombosis after infection with the respiratory viruses influenza A virus and coronavirus. J Thromb Haemost 2021 online ahead of print. doi:10.1111/jth.15509.
17. Zelaya H, Rothmeier AS, Ruf W. Tissue factor at the crossroad of coagulation and cell signaling. J Thromb Haemost 2019;16:1941–52.
18. Antoniak S, Mackman N. Multiple roles of the coagulation protease cascade during virus infection. Blood 2014;123:2605–261317.
19. Sutherland MR, Ruf W, Pryzdial ELG. Tissue factor and glycoprotein C on herpes simplex virus type 1 are protease-activated receptor 2 cofactors that enhance infection. Blood 2012;119:3638–45.
20. Sutherland MR, Simon AY, Shanina I, et al. Virus envelope tissue factor promotes infection in mice. J Thromb Haemost 2019;17:482–91.
21. Lee AY, Vlasuk GP. Recombinant nematode anticoagulant protein c2 and other inhibitors targeting blood coagulation factor VIIa/tissue factor. J Intern Med 2003;254:313–21.
22. Geisbert TW, Hensley LE, Jahrling PB, et al. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys. Lancet 2003;362:1953–8.
23. Giugliano RP, Wiviott SD, Stone PH, et al. Recombinant nematode anticoagulant protein c2 in patients with non-ST-segment elevation acute coronary syndrome: the ANTHEM-TIMI-32 trial. J Am Coll Cardiol 2007;49: 2398–2407.
24. Moons AH, Peters RJ, Bijsterveld NR, et al. Recombinant nematode anticoagulant protein c2, an inhibitor of the tissue factor/factor VIIa complex, in patients undergoing elective coronary angioplasty. J Am Coll Cardiol 2003;41: 2147–2153.
25. Lee A, Agnelli G, Buller H, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. Circulation 2001;104:74–8.
26. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19: Final report. N Engl J Med 2020;83:1813–26.
27. Klok FA, Boon G, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020;56:2001494.
28. Khoufache K, Berri F, Nacken W, et al. PAR1 contributes to influenza A virus pathogenicity in mice. J Clin Invest 2013;123:206–14.
29. Aerts L, Hamelin ME, Rheaume C, et al. Modulation of protease activated receptor 1 influences human metapneumovirus disease severity in a mouse model. PLoS One 2013;8:e72529.
30. Garcia-Carrasco M, Mendoza-Pinto C, Macias-Diaz S, et al. The role of infectious diseases in the catastrophic antiphospholipid syndrome. Autoimmun Rev 2015;14:1066–71.
31. Muller-Calleja N, Hollerbach A, Ritter S, et al. Tissue factor pathway inhibitor primes monocytes for antiphospholipid antibody-induced thrombosis. Blood 2019;134:1119–31.